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Status of diagnostic approaches to AQP4-IgG seronegative NMO and NMO/MS overlap syndromes

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Abstract

Distinguishing aquaporin-4 IgG (AQP4-IgG)-negative neuromyelitis optica spectrum disorders (NMOSD) from opticospinal predominant multiple sclerosis (MS) is a clinical challenge with important treatment implications. The objective of the study was to examine whether expert clinicians diagnose and treat NMO/MS overlapping patients in a similar way. 12 AQP4-IgG-negative patients were selected to cover the range of clinical scenarios encountered in an NMO clinic. 27 NMO and MS experts reviewed their clinical vignettes, including relevant imaging and laboratory tests. Diagnoses were categorized into four groups (NMO, MS, indeterminate, other) and management into three groups (MS drugs, immunosuppression, no treatment). The mean proportion of agreement for the diagnosis was low ($p_o = 0.51$) and ranged from 0.25 to 0.73 for individual patients. The majority opinion was divided between NMOSD versus: MS (nine cases), monophasic longitudinally extensive transverse myelitis (LETM) (1), acute disseminated encephalomyelitis (ADEM) (1) and recurrent isolated optic neuritis (RION) (1). Typical NMO features (e.g., LETM) influenced the diagnosis more than features more consistent with MS (e.g., short TM). Agreement on the treatment of patients was higher ($p_o = 0.64$) than that on the diagnosis with immunosuppression being the most common choice not only in patients with the diagnosis of NMO (98 %) but also in those indeterminate between NMO and MS (74 %). The diagnosis in AQP4-IgG-negative NMO/MS overlap syndromes is challenging and diverse. The classification of such patients currently requires new diagnostic categories, which incorporate

lesser degrees of diagnostic confidence. Long-term follow-up may identify early features or biomarkers, which can more accurately distinguish the underlying disorder.

Keywords

All demyelinating disease (CNS); Multiple sclerosis; Devic's syndrome; Optic neuritis; Transverse myelitis

Introduction

NMO, previously considered a variant of MS, is characterized by severe attacks of transverse myelitis (TM) and optic neuritis (ON) [1]. The discovery of AQP4 antibodies as a highly specific biomarker separated NMO from MS and led to its recognition as a distinct disease [2, 3]. It also broadened the clinical spectrum of NMO as AQP4 antibodies are found in limited forms of NMO such as isolated longitudinally extensive transverse myelitis (LETM), isolated optic neuritis, and in brain/brainstem syndromes previously not linked with NMO, such as the area postrema (AP) syndrome [1]. These syndromes are termed NMO spectrum disorders (NMOSD) and are managed as NMO [4]. This poses important challenges in patients who test negative for AQP4 antibodies, since most of these syndromes are not specific for NMO and are also encountered in MS or other demyelinating disorders [5, 6]. Accurate diagnosis is, however, essential to minimize harm from inappropriate treatment as NMO drugs are not licensed for MS and MS therapy might severely exacerbate NMO [7–11].

In this study, we aimed to examine whether NMO and MS clinicians diagnose and treat antibody-negative NMO/MS overlapping patients in their everyday clinical practice in a similar way.

Methods

Study design

27 Neurology Consultants with expertise in inflammatory demyelinating diseases of the CNS scored 12 anonymised case histories of patients with AQP4-Ab-negative NMO or MS-like syndromes who had been referred to the Oxford NMO service. All experts received brief clinical summaries of each patient with relevant investigation results (see Online Resource 1) and a questionnaire (see Online Resource 2) and were asked to give their working diagnosis and how they would treat the patient in real life. All experts were allowed to ask for additional information if they felt this would help them in their decision-making process.

Clinical cases

We selected patients with clinical presentations with overlapping features of NMO and MS, because these patients pose particularly difficult diagnostic (and hence management) challenges. Patients were selected to represent different and representative clinical dilemmas.

The clinical summaries were anonymised and contained the most relevant clinical information available such as age, sex, ethnicity, attack features, recovery from attacks, disability level, relapse and long-term treatment, laboratory test results (including myelin oligodendrocyte glycoprotein (MOG) antibody status where tested [12–14]), visual-evoked potentials (VEP) and brain and spinal cord MRI imaging summary reports with selected images showing lesions. The details of these cases as sent to the clinicians are set out in Online Resource 1.

Analysis

Experts' opinions were categorized into four diagnostic categories (MS, NMO/NMOSD, indeterminate between MS and NMO, other) and into three treatment categories (MS disease modifying-therapies (DMTs), chronic immunosuppression (including rituximab and regular plasma exchange (PLEX), no treatment). The main results are described qualitatively.

Proportion of observed agreement (p_o) was calculated to assess the extent to which raters agreed for an individual patient. This was measured as the number of rater–rater pairs in agreement relative to the number of all possible rater–rater pairs [15]. A p_o value of 1 corresponds to complete agreement between raters. The lowest possible (i.e., arising by chance) p_o for 27 raters and four categories is 0.22 (seven assignments to three categories and six assignments to one category), while for three categories, the lowest possible score was 0.31 (nine assignments to each category).

Mean p_o and Fleiss kappa (κ) were used to assess inter-rater agreement in the whole cohort of patients [15]. $\kappa < 0$ indicates poor agreement, 0.01–0.20 slight, 0.21–0.40 fair, 0.41–0.60 moderate, 0.61–0.80 substantial and 0.81–1.0 almost perfect agreement [16].

To compare kappa for treatment with kappa for diagnosis, we reduced the number of categories for diagnosis to three by merging 'indeterminate between MS and NMO' and 'other' into one category.

To assess the influence of local MS prevalence on diagnostic decisions, experts were divided into two groups: the 21 practising in countries with high MS prevalence (Australia, Belgium, Denmark, France, Germany, Ireland, Poland, United Kingdom, United States), and the six from medium or low MS prevalence countries (Portugal, Turkey, India, Japan, South Korea) [17]. Non-parametric Mann–Whitney U test was used to assess if the location of the expert influenced the likelihood of making a diagnosis of MS.

Analyses were conducted using SPSS 22.0 (SPSS Inc, Chicago, IL) and Microsoft Excel (Microsoft Corp, Redmond, WA).

Definition of NMO-typical and MS-typical features

To explore clinical and paraclinical features most strongly associated with choice, we focused on well-established discriminators between NMO and MS [5]. LETM, severe ON (i.e., with visual acuity worse than 6/36 in at least one eye at recovery), bilateral simultaneous ON, simultaneous ON and TM, NMO-like brain lesions (i.e., adjacent the floor of 3rd or 4th ventricle, periaqueductal lesions, diffuse lesions in the splenium [18, 19]) were

considered as typical of NMO, while short TM, mild ON (i.e., with visual acuity 6/36 or better at recovery), unmatched OCB in the CSF and MS-like brain lesions (lesions adjacent to lateral ventricles, Dawson's fingers, juxtacortical S-shaped lesions were considered as typical of MS and being able to distinguish MS from NMO [6]). The combination of these features was not explored because of the small numbers of cases, although integration of these observations is important in reaching a diagnosis, as none are considered either pathognomonic or exclusionary for either diagnosis.

Results

Diagnosis

High disagreement among expert clinicians—Figure 1 shows a brief clinical summary with the different diagnoses and treatment choices scored by the experts for each patient. Diagnoses alternative to MS and NMO ('other') included relapsing isolated ON (RION)/chronic relapsing inflammatory ON (CRION) (23 opinions), idiopathic LETM (20), acute disseminated encephalomyelitis (ADEM, 14), recurrent TM (4), neurosarcoidosis (2), vasculitis (1), Leber hereditary optic neuropathy (1), antiphospholipid syndrome (APLS, 1) and lupus (1). NMO(SD) was the most common diagnosis in seven patients, MS in two patients and other in three patients (LETM, ADEM, CRION). The p_o for individual patients ranged from 0.25 to 0.73 (Table 1). Mean p_o was 0.51 and overall Fleiss κ was 0.27 indicating fair agreement between experts.

The association between individual features and an individual clinicians

diagnosis—Amongst our patients, 3/12 had at least one MS-typical feature but no NMO-typical features (Table 2) and in these MS was diagnosed more commonly than NMO (58 % opinions versus 23.5 %, Fig. 2a). Four of 12 cases had at least one NMO-typical feature but no MS-typical features and the diagnosis of NMO was more frequent (44.4 versus 0.9 %). Five of 12 had features typical both of MS and NMO, and NMO was diagnosed more often than MS (61.5 versus 22.9 %) demonstrating that in expert clinical assessment NMO characteristics overrode the MS-typical features.

We found that in patients with LETM (5/12), an NMO diagnosis was significantly more prevalent (60.7 % opinions) than MS (6.7 %, Fig. 2b). After excluding monophasic patients, this difference was even more striking (NMO 80.2 versus MS 9.9 %, Fig. 2b). The majority of clinicians (74 %) did not diagnose MS in patients with LETM (Online Resource 3, eTable 1). However, short spinal cord lesions did not preclude the diagnosis of NMO by the experts.

The presence of severe residual visual loss from ON would be associated with an MS diagnosis by only 22 % of clinicians (Online Resource 3, eTable 2) and bilateral ON was associated with an MS diagnosis by only one clinician (eTable 3). However, complete recovery from ON was felt to be compatible with NMO by the majority of clinicians (eTable 2).

Although small numbers of patients had brain MRI changes, the one patient with MS-typical lesions was diagnosed as MS by 85 % of experts and in the two cases with typical NMO lesions NMO was diagnosed by 74 % of experts, eTable 4).

The presence or absence of OCB in the CSF did not appear to strongly influence the diagnosis; 93 % of clinicians were comfortable in making at least one diagnosis of NMO in those with OCBs, and 70 % in making at least one MS diagnosis in those with absent OCBs (eTable 5).

44 % of clinicians made a diagnosis of clear NMO in monophasic disease, but another 56 % felt this was another disease.

Influence of NMO diagnostic criteria on NMO diagnosis—We further assessed how the 2006 [20] (and the new 2015 [21]; Table 3) NMO criteria impact expert diagnosis. 2006 and new NMO criteria were both fulfilled by three patients (Fig. 1—Patient 7, 8, 11). Mean proportion of NMO diagnosis in these patients was 80 % (range 78–85 %, Table 4). Alternative diagnoses included MS (9.9 % of opinions) and other (6.2 %), i.e., neurosarcoidosis, vasculitis, APLS and lupus. Eleven experts made at least one non-NMO diagnosis in patients fulfilling the NMO criteria and 22 experts felt comfortable in diagnosing NMO in patients who did not fulfill the criteria. For the nine patients who did not fulfill the criteria, mean proportion of NMO diagnosis varied between 4 and 63 % (Online Resource 3, eTable 6). Only three experts fully conformed to the diagnostic criteria in their answers.

Sources of diagnostic disagreement—Experts' comments have been analyzed to identify sources of disagreement in cases with most diverse diagnoses (i.e., six patients characterized by a $p_o < 0.5$). In five of these cases, experts disagreed mainly between NMO and MS and in one case (patient 12) mainly between NMO and ADEM. Sources of disagreement are presented in Table 4. The sources of disagreement varied between the cases; patient 5 and 9 had mixed typical features of both MS and NMO, patient 4 had typical clinical MS features not backed by brain MRI, and patient 3 had brain lesions not completely typical of NMO or MS and a spinal cord lesion of approximately three vertebral segments that would be considered indeterminate or borderline (Fig. 3).

We were also interested to see whether local MS prevalence might have influenced experts' diagnostic decisions. We found that experts from countries characterized by low or medium MS prevalence diagnosed MS less frequently than those from areas with high prevalence of MS (Online Resource 4, $p = 0.01$).

Treatment

Treatment recommendations—We further analyzed how experts would manage these patients. In the total cohort of 12 patients, 64.8 % of opinions recommended immunosuppression, 18.8 % DMTs and 16.4 % none (or 'watch and wait'). Treatment options for individual patients are shown in Fig. 1. Mean p_o for treatment was 0.64 and κ was 0.30 (Online Resource 3, eTable 7). After reducing the number of categories to three for diagnosis (MS, NMO, indeterminate/other), we found that both mean p_o and inter-rater κ for treatment are higher in comparison to those for diagnosis (mean p_o for three diagnostic categories 0.53, κ 0.26). Thus, experts appeared to agree more on the management of patients than on the diagnosis often choosing immunosuppression as the preferred option.

How the diagnosis affects the treatment choice—Where a diagnosis of NMO was made, immunosuppression was selected in 97 % of cases whereas a no treatment strategy was selected in the remainder. Where MS was diagnosed, 73 % opinions pointed to DMTs, 18 % to immunosuppression and 9 % to no treatment. If MS DMTs were selected, first-line MS drugs (IFN- β , glatiramer) were generally preferred (79 %) to second-line drugs (natalizumab, fingolimod). In patient 3 who had an aggressive disease with active brain lesions, ten experts diagnosed MS and of these the majority went for second-line DMTs. Where the diagnosis was indeterminate between MS and NMO (27 opinions, 9/12 patients), immunosuppression was selected in 74 % of opinions, no treatment in 22 % and DMTs in 4 %. In two patients who had monophasic disease, 28 % of opinions suggested chronic treatment with immunosuppression (26 %) or MS DMT (2 %).

Discussion

Our study shows that experts frequently disagreed on the diagnosis of AQP4-Ab-negative NMO/MS overlapping patients. The majority opinion was divided between MS versus NMO(SD), but also NMOSD versus monophasic LETM [22, 23], NMOSD versus RION/CRION, and NMOSD versus ADEM. The presence of typical NMO features, such as LETM or severe ON, was associated with a low rate of MS diagnosis, even if MS features were also present. When NMO features occurred without MS features, experts often pointed to diagnoses alternative to NMO(SD), such as CRION, or in monophasic patients ADEM or idiopathic LETM. There was a lack of consensus on diagnosis of monophasic syndromes consistent with NMOSD. Some consultants considered them as indeterminate monophasic events (LETM, ADEM), while others diagnosed NMOSD. NMO was typically diagnosed in those who fulfilled NMO criteria but it was also considered in those who did not fulfill them. Immunosuppression was the first-choice treatment in almost all NMO(SD) patients, most patients indeterminate between MS and NMO, and also in some MS patients. MS DMTs were typically recommended in patients with the diagnosis of MS but were generally avoided in patients indeterminate between NMO and MS.

Frequent disagreement among experts regarding the diagnosis indicates that borders between AQP4-negative NMOSD and other inflammatory conditions of the CNS are poorly demarcated. This also reflects the wide differential in antibody-negative NMOSD [13]. Combinations of NMO and MS features (e.g., severe ON and short TM) are not uncommon in patients referred to an NMO clinic and if strong NMO/MS discriminators are lacking, accurate diagnosis is challenging.

Not surprisingly, LETM is a potent NMO/MS discriminator and it strongly drives the diagnosis toward NMO(SD), particularly if it occurs in the context of a relapsing disease. But this is dependent on availability of spinal cord imaging at the time of an acute myelitis event; imaging in remission may fail to demonstrate a LETM. It is also worth emphasizing that a number of different diseases can cause LETM [22, 23]. In a recent large series of LETM patients presenting to an NMO service, diagnoses alternative to NMO could be identified even in those fulfilling the NMO diagnostic criteria, and only 6.5 % of patients had “true” seronegative NMO and 6.5 % had idiopathic LETM [23]. On the other hand, the initial myelitis episode in NMO(SD) is accompanied by a short lesion in approximately

14 % of AQP4-Ab-positive cases [24], which might explain frequent NMO diagnoses in short TM patients in our study. While relapsing AQP4-Ab-negative disease with LETM is generally considered within the NMO(SD), relapsing severe ON is often recognized as distinct from NMOSD and termed RION or CRION by many experts [25, 26]. Interestingly, CSF OCB was not strongly influential and this is probably because other features were felt to be more important.

Fulfillment of the diagnostic criteria was not considered obligatory by the majority of experts (89 %) and individual raters appeared to have different thresholds for overriding them. Some experts accepted spinal cord lesions shorter than three segments or abnormal brain MRI which would fulfill Paty criteria as compatible with NMO [20, 27]. Also typical NMO-like brain lesions appeared to override other criteria in some cases.

Despite diagnostic difficulties experts tend to agree that when there is a serious doubt about the diagnosis and NMO is a possibility, immunosuppression is the most prudent option. This might explain frequent decisions to use this modality to treat not only indeterminate cases but also those diagnosed with MS. This approach reflects a general opinion supported by several reports that MS drugs (notably interferon β , natalizumab and fingolimod) might dramatically exacerbate NMO [7, 8, 10, 28–30], whereas there is evidence that immunosuppression might be efficacious in MS [31–34]. The drugs most commonly used for overlap syndromes in our clinical practice include azathioprine, mycophenolate and rituximab.

There are several limitations to this study. First of all, the quantitative analysis cannot be applied to other clinical settings because the patients were pre-selected to cover a range of challenging clinical scenarios and are not representative of unselected MS or NMO clinic populations. However, this study was deliberately exploring the agreement of experts within this selected group of patients. The local prevalence of differential diagnosis might have affected how experts rated our cases and therefore could have contributed to the disagreement. This was supported by the observation that experts from countries with low or medium MS prevalence less frequently diagnosed MS compared with those from high MS prevalence areas. Of note, the predictive value of diagnostic criteria in general depends on the local prevalence rates of the condition. Another concern could be that clinical vignettes provide limited information on patients in comparison to a face-to-face experience and full access to medical records. This approach should not, however, increase the disagreement as all experts were presented with the same information, which would more likely reduce variation produced by differences in individual experts' clinical experience and style. Despite its possible limitations, well-constructed clinical vignettes are considered the best tool to evaluate the clinical practice in real-life settings and to perform comparative analysis among medical centers or health care systems [35].

Significant disagreement on the diagnosis of AQP4-Ab-negative NMO/MS overlapping syndromes has important therapeutic implications as treatments for both diseases differ and with a rapid progress in the field of MS/NMO therapy, they are likely to become even more exclusive in the upcoming years. More work is required to subdivide AQP4-Ab-negative NMOSD so that clinicians could clearly classify patients according to phenotype with more

agreement. This could be instituted by allowing different degrees of certainty such as 'possible', 'probable' or using other terms such as 'undefined' or 'mixed', and would be particularly useful in monophasic phenotypes with short follow-up times and in those with mixed NMO and MS features. Limited forms of NMO (NMOSD), which are particularly challenging, are currently not recognized by NMO criteria. However, it is clear from this study that clinicians regard limited forms of NMO as a similar entity to this with both ON and TM. MOG Abs identified in some AQP4-Ab-ve patients might define a distinct, probably milder form of NMO and help differentiating it from MS [12–14, 36]. In those who are double negative, the accurate diagnosis may demand longitudinal follow-up. Further prospective studies on patients defined both on clinical/radiological characteristics and serology results are needed to develop diagnostic algorithms and determine the ultimate diagnosis in this group of patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1.
Short descriptions of patients' clinical presentation and 100 % stacked bar charts showing variability of opinions concerning the diagnosis and treatment of patients

Fig. 2.

a Mean proportion of distinct diagnoses in patients who had at least one MS-typical feature but none of NMO-typical features, those who had at least one NMO-typical feature but none of MS-typical features and those who had both types of features (as in Table 2). **b.** Mean proportion of distinct diagnoses in patients who had LETM, patients who had LETM as a part of a relapsing disease and those who had ON with poor recovery

Fig. 3. Examples of MRI images with mixed features of MS and NMO. Patient 3 had borderline LETM (**a**, *arrow*) and a gadolinium-enhancing well-demarcated juxtacortical lesion not typical of NMOSD (**b**, *arrow*). Patient 5 had a central spinal cord lesion shorter than three segments (**c**, *arrow*) and a lesion in the floor of 4th ventricle considered typical of NMOSD by most experts (**d**). All MRI images, which were available for experts, are included in Online Resource 1

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Table 1
Agreement table for diagnosis with the number of ratings for individual patients and measures of inter-rater agreement

	MS	NMO	Indeterminate	Other	p_o
Pt. 1	16	5	5	1	0.40
Pt. 2	23	1		3	0.73
Pt. 3	10	14	2	1	0.39
Pt. 4	8	13	4	2	0.32
Pt. 5	7	17	3		0.46
Pt. 6		6		21	0.64
Pt. 7	5	21	1	0	0.63
Pt. 8	3	21	1	2	0.61
Pt. 9	6	10	7	4	0.25
Pt. 10		8		19	0.57
Pt. 11		23	1	3	0.73
Pt. 12	1	11	3	12	0.35
Proportion of diagnosis	0.24	0.46	0.08	0.21	
Mean p_o					0.51
κ					0.27

Bold values indicate inter-rater agreement parameters for the whole cohort of patients

Table 2
The presence of typical MS-like and NMO-like features in 12 cases selected for the project

Patient	MS features			NMO features				NMO or MS features		
	Mild ON	Short TM	MS brain	OCB	Severe ON	BON	Simultaneous ON + TM	LETM	NMO brain	
1	+	+	-	-	-	-	-	-	-	MS
2	-	+	+	+	-	-	-	-	-	MS
3	+	-	-	-	-	-	-	±	-	Both
4	+	+	-	-	-	-	-	-	-	MS
5	+	-	-	+	-	-	-	±	+	Both
6	-	-	-	-	-	-	-	+	-	NMO
7	+	-	-	+	-	-	-	+	-	Both
8	+	-	-	+	-	-	-	+	-	Both
9	-	+	-	+	+	-	-	-	-	Both
10	-	-	-	-	+	-	-	-	-	NMO
11	-	-	-	-	-	+	-	+	+	NMO
12	-	-	-	-	+	-	+	+	-	NMO

Table 3

New revised diagnostic criteria for NMOSD without AQP4-Ab

Requirements	Core clinical characteristics
At least two core clinical characteristics all satisfying: 1 of ON, myelitis, or area postrema syndrome Dissemination in space Additional MRI requirements (AP syndrome: dorsal medulla lesion; myelitis: LETM; ON: normal brain MRI or [1/2 ON or chiasm lesion) No better explanation for the clinical syndrome	Optic neuritis Acute myelitis Area postrema syndrome Other brainstem syndrome Symptomatic narcolepsy or acute diencephalic syndrome with MRI lesion(s) Symptomatic cerebral syndrome with MRI lesion(s) typical of NMOSD

Table 4

Clinical presentations associated with very low agreement ($p_0 < 0.5$) on the diagnosis

ON with limited recovery and short TM
Mild ON and short TM with normal brain MRI
ON and borderline LETM
ON and TM with brain lesions not fully typical of MS or NMO
Monophasic ADEM-like disease with ON and LETM

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